REMARKS/ARGUMENTS

This Office Action is a FINAL Action in which the Examiner has objected to claims 24, 26, 27 and 30 under 35 U.S.C. 112, first paragraph.

First, applicant has cancelled claim 26 rendering the objection to this claim moot.

Applicant would like to draw the Examiner's attention to the fact that the mice used in the experiments were challenged with peripheral blood lymphocytes (PBL) and not platelets as stated by the Examiner in the first sentence of paragraph 6 of the Office Action *"...with respect alloimmunization to platelet transfusions..."*.

The Examiner argues that the claims are broader than the teaching of the descriptions because *"...targeted end points and diseases are not limited to inhibiting alloimmunization of anti-HLA antibody responses..."*. Applicant has amended claims 24 and 30 to recite a method for inhibiting an anti-HLA alloimmune antibody response. This amendment clearly overcomes the concern of the Examiner in view of the breadth of the claims.

Before proceeding and addressing the further objections raised in the Office Action, applicant would like to clarify some of the statements made at the bottom of page two of the Office Action, in which the Examiner summarizes the state of the prior art regarding the 18KDa CD40L molecule. In particular, the last sentence of page 2 states *"therefore, the instant claims are limited to the soluble CD40L to a known oligomeric CD40L agonists and away from the referenced soluble monomeric CD40L antagonists."* Applicant respectfully submits that the CD40L of the present invention is indeed oligomeric but is an antagonist. These oligomeric CD40L antagonists are different from the prior art since the prior art suggests monomeric CD40L antagonists.

These facts are correctly stated by the Examiner at the first paragraph of page three of the Office Action in which it is stated that *"...oligomeric 18KDa CD40L is an antagonist rather than a CD40 agonist..."*.

Applicant respectfully points out that the Examiner incorrectly stated in the first paragraph of page 3 of the Office Action that the immunization model is a platelet HLA alloimmune immunization model. The model is a PBL model as explained above.

The Examiner then raises the issue of the correlation between in vitro and animal model studies and in vivo clinical trial results in patients. Applicant refers the Examiner to our previous response in which a Declaration from the inventor confirming that the presently used humanized in vivo animal model is an accepted model in the present art. This evidence was provided along with references of the art indicating that such a model correlates with the inhibition of human alloimmune response.

The Examiner further states that *"there is insufficient objective evidence that accurately reflects the relative efficacy of the claimed therapeutic strategies to inhibit alloimmune responses, T cell responses, autoimmune diseases, commensurate in scope with the therapeutic methods encompassed by the claimed methods."*

Applicant submits that newly amended claims, which now recite a method for inhibiting an anti-HLA alloimmune antibody response, are supported by sufficient and objective evidence in the specification. More specifically, it is clearly indicated in Figure 1B that mice reconstituted with human peripheral blood lymphocytes and injected with 18KDa CD40L protein, exhibit much reduced production of alloantibodies. (See description of Figure 1 at page 9, line 27-35). Thus, clearly there is sufficient and objective evidence that the use of soluble 18KDa recombinant in humans CD40L can inhibit an anti-HLA alloimmune antibody response.

Furthermore, the results presented in the present disclosure argue against the reason a pharmaceutical therapy might be unpredictable as listed by the Examiner in the Office Action. Namely, the protein was obviously not degraded before it produced an affect since the hoped-for effect was indeed observed in the experiments; the protein (18KDa CD40L) obviously reached the target area since again an effect was observed; while it is not known whether the protein would have prohibited side effects in humans, it is clear that it did not have such effect in mice since the mice were followed up to a month or more after treatment without noticeable toxicity. Therefore, it is respectfully submitted that a person

skilled in the art would appreciate that the results in the application can be used to infer that successful in vivo therapeutic use would be predictable.

The next paragraph in the Office Action (paragraph 5 of page 3), again incorrectly states that the 18KDa CD40L molecule of the present invention is a CD40 agonist. It is respectfully submitted as explained *supra* that the CD40L of the present invention is an oligomeric antagonist.

Therefore, the molecule of the present invention would definitely not act as an agonist and would not have the opposite effect. The result clearly indicates that it is an antagonist that has the desired effect. The arguments elaborated by the Examiner based on the prior art, in particular Aruffo et al., have been addressed in a previous response. Briefly, it was argued that Aruffo et al. uses soluble ligands of CD40L (not ligands to CD40) to prevent the interaction between T cells and B cells. In contrast, the present invention is to a CD40 ligand (CD40L). In any event, the data presented in the present disclosure clearly indicates that the 18KDa CD40L is an antagonist that reduces the production of alloantibodies.

With regard to the Armitage reference, again it is submitted that the CD40L disclosed therein is a monomeric antagonist in contrast with the present invention which describes an oligomeric antagonist.

In the next paragraph in the Office Action (paragraph 3 of page 4), the Examiner notes that the mechanism of action by which 18KDa CD40L exerts its action is unclear and states in the second last sentence that *"soluble 18KDa CD40L appears limited in the conditions of inhibiting alloimmune response or T cell immune responses."* Applicant submits that the results clearly indicate that 18KDa CD40L inhibits the production of alloantibodies and this is the desired results. The manner in which it does so seems irrelevant to the patentability of the claims. Even if the mechanism of action is unclear, the desired results are reached when the method as claimed in the pending claims is applied.

The CD40L described in Nannizzi Alaimo et al. is clearly an agonist (see third paragraph of discussion) in contrast with the 18KDa CD40L of the present invention which is an antagonist. Therefore, Nannizzi Alaimo et al. is not relevant to the present claims.

The Examiner then objected to claim 30 on the grounds that there is insufficient objective evidence that the claim soluble 18KDa CD40L can prevent the diseases listed in said claim. Applicant respectfully traverses this objection on the grounds that 18KDa CD40L of the present invention inhibits the production of alloantibodies, in that this inhibition would be understood to occur irrespective of the condition being treated. That is to say, any condition that would lead to the alloantibody would benefit from treatment with 18KDa CD40L. However, should the Examiner persist in his rejection, he is respectfully enjoined to consider the patentability of new claim 34 which is drawn to one specific disease listed in claim 30, namely graft vs host disease. It is respectfully submitted that no new subject matter is added in the newly provided claim.

Therefore, in view of the above, applicant contends that the in vivo results from humanized animal models clearly provide sufficient predictability and enablement to practice the invention as claimed in the newly amended claims.

With regard to the comments made at page 5 of the Office Action to the effect that the Examiner invites the applicant to consider amending the claims to recite limitation that read on platelet alloimmunization, it is respectfully submitted, as discussed with the Examiner, that the experiments were performed using peripheral blood lymphocytes (not platelets) to challenge the mice.

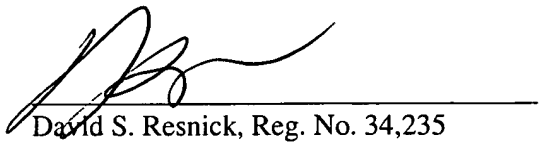
Applicant now addresses claim 27. The claim is directed at a method for inhibiting T cell function in an anti-HLA alloimmune response in a patient. The disclosure at page 25 starting at line 8 provides sufficient and objective results supporting the inhibition of T cell function by 18KDa CD40L. This is a useful, new and non-obvious observation since an alloimmune response is not necessarily restricted to the production of antibodies and may involve T cells. Therefore, the observation that T cell function can be inhibited by 18KDa CD40L is clearly patentable.

In view of the above, it is believed that the claims are now in condition for allowance.

Favorable reconsideration and Allowance are therefore respectfully requested.

Date: September 17, 2004

Respectfully submitted,
NIXON PEABODY LLP



David S. Resnick, Reg. No. 34,235
Nixon Peabody LLP
100 Summer Street
Boston, MA 02110-2131
(617) 345-6057